

**1/1**

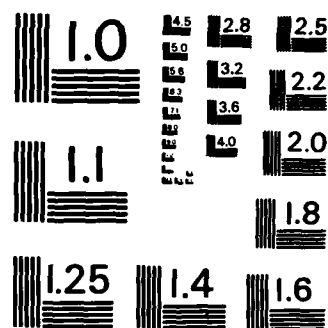
F/G 6/5

NL

END

FILMED

DTIC



MICROCOPY RESOLUTION TEST CHART  
NATIONAL BUREAU OF STANDARDS-1963-A



2

# ONRL Report

R-3-85

AD-A158 951

Biomaterials Research in West Germany--An Assessment

Thomas C. Rozzell

14 August 1985

Accession For

NTIS GRA&I

DTIC TAB

Unannounced

Justification

By

Distribution/

Availability Codes

Dist

Avail and/or  
Special

A-1



DTIC  
ELECTE  
SEP 10 1985  
S  
D  
E

Approved for public release; distribution unlimited

U.S. Office of Naval Research, London

DTIC FILE COPY

85 9 09 05 1

ADA 158 951

# REPORT DOCUMENTATION PAGE

1a REPORT SECURITY CLASSIFICATION <b>UNCLASSIFIED</b>			1b RESTRICTIVE MARKINGS	
2a SECURITY CLASSIFICATION AUTHORITY			3 DISTRIBUTION AVAILABILITY OF REPORT <b>Approved for public release; distribution unlimited</b>	
2b DECLASSIFICATION / DOWNGRADING SCHEDULE				
4 PERFORMING ORGANIZATION REPORT NUMBER(S) <b>R-3-85</b>			5 MONITORING ORGANIZATION REPORT NUMBER(S)	
6a NAME OF PERFORMING ORGANIZATION <b>US Office of Naval Research Branch Office, London</b>		6b OFFICE SYMBOL (If applicable) <b>ONRL</b>	7a NAME OF MONITORING ORGANIZATION	
6c ADDRESS (City, State, and ZIP Code) <b>Box 39 FPO, NY 09510</b>			7b ADDRESS (City, State, and ZIP Code)	
8a. NAME OF FUNDING / SPONSORING ORGANIZATION		8b. OFFICE SYMBOL (If applicable)	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER	
8c. ADDRESS (City, State, and ZIP Code)			10 SOURCE OF FUNDING NUMBERS	
			PROGRAM ELEMENT NO	PROJECT NO
			TASK NO	WORK UNIT ACCESSION NO
11 TITLE (Include Security Classification) <b>Biomaterials Research in West Germany-- An Assessment</b>				
12 PERSONAL AUTHOR(S) <b>Thomas C. Rozzell</b>				
13a. TYPE OF REPORT <b>Technical</b>	13b. TIME COVERED FROM _____ TO _____	14 DATE OF REPORT (Year, Month, Day) <b>14 August 1985</b>	15 PAGE COUNT <b>13</b>	
16 SUPPLEMENTARY NOTATION				
17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)	
FIELD	GROUP	SUB-GROUP	<b>Biomaterials</b> <b>West Germany</b> <b>Wound healing,</b> <b>Tissue repair</b> <b>Drug delivery</b> <b>Prosthesis</b> <b>Implants,</b>	
<b>06</b>	<b>05</b>			
19 ABSTRACT (Continue on reverse if necessary and identify by block number)				
<p>West Germany is one of the leading countries in Europe for research in biomaterials. Researchers have developed a number of new techniques and methods utilizing a wide range of synthetic and natural materials for use in medicine. Exotic ceramics, metals, and plastics are being used both in animals and in humans for such things as tissue repair, wound coverings, drug delivery, and prostheses. The West German scientists, bioengineers, and clinicians are very aggressive in attacking new problems related to the use of biomaterials in therapy. <i>Originator supplied keywords include:</i></p>				
20 ABSTRACT SECURITY CLASSIFICATION <b>UNCLASSIFIED</b>			21 ABSTRACT SECURITY CLASSIFICATION <b>UNCLASSIFIED</b>	
22a NAME OF RESPONSIBLE INDIVIDUAL <b>Larry E. Shaffer</b>			22b TELEPHONE (Include Area Code) <b>(44-1) 409-4340</b>	22c OFFICE SYMBOL <b>11</b>

## BIOMATERIALS RESEARCH IN WEST GERMANY-- AN ASSESSMENT

### 1 INTRODUCTION

West Germany is one of the most aggressive countries in Western Europe in research and technology. This is not by accident, as programs have been purposefully designed to overcome a perceived lag in research going back before the beginning of World War II. In this report, I will first examine some of the elements of the research support structure of West Germany, with particular emphasis on biological and medical sciences. Then, I will attempt to give an overview and assessment of the current research in biomaterials.

As in most countries of the Western world, research in West Germany is conducted in three major sectors: the universities, nonuniversity institutions, and industry. Besides the usual situations of university scientists working as researchers and lecturers, there are a few instances where small institutes have been formed within universities, and individuals are able to carry out research without the extra burden of lectures.

There seems to be no good estimate available on the amount of money actually spent on research each year in West Germany. Research and teaching at the universities and research development in industry are so closely linked that it is impossible to identify the expenditure that goes only to research. It is clear that the figure is well over DM35 billion (\$11.3 billion). Apparently, half of this money comes from private industry and half from the state.

By "state" is meant not one central government but a number of more or less autonomous agencies. The universities are self-governing, and the federally financed large science centers work by and large independently. There are a number of ways in which public monies flow into research. One of these is through the German Research Society (Deutsche Forschungsgemeinschaft, DFG).

The DFG is the central self-governing organization of science and the humanities in West Germany. It is charged with promoting all areas of science. Thus it supports research in every discipline, especially basic and applied research as practiced in the universities and technical academies. The DFG pays particular attention to support of investigators who have received the doctorate within the past 5 years. In its promotion of research, the DFG funds individual projects, cooperative programs, central research facilities, etc. There are also grants for training and travel, especially for young investigators who are not yet established in their field. Special collaborative programs have been established which involve groups of scientists who have, with the approval of their universities, combined their efforts so as to pursue joint research in areas where the respective universities recognize a focal point of activity that calls for long-term support. These programs aim at concentrating personnel and facilities, planning and coordination of research within and under the supervision of the universities, and interdisciplinary cooperation.

In addition, the DFG supports research by funding scientific libraries, providing computers for data processing centers, providing general scientific apparatus for laboratories, and reviewing applications for equipping research centers within the framework of the law for improvement of university facilities. The DFG also represents German science on the international level. It coordinates and finances the German share in major international research programs.

Like the US National Academy of Sciences, the DFG provides a broad range of advice on scientific matters to various government authorities. It has a large number of commissions and committees of experts that furnish basic information for use in making laws involving the environment and public health.

In summary, the DFG appears to combine many of the functions of the National Science Foundation, the National Academy of Science, and the National Institutes of Health in the US. In 1984, the DFG had a budget in excess of DM900 million (\$290 million), of which more than 55 percent went directly to support young scientists.

In contrast to the DFG, a pure fund-distributing organization, the Max Planck Society for the Advancement of Science (Max-Planck-Gesellschaft zur Förderung der Wissenschaften, MPG) actually operates its own institutes, 50 in all. Most of these institutes conduct basic research in the natural sciences and many have been world renowned for decades. The MPG is financed primarily by the federal and local governments. However, a number of projects are supported through grants and contracts from industry or foreign governments. The MPG is known throughout the world for the excellence of its research.

The Max Planck institutes devote their attention to new problems which are not yet sufficiently developed for university research or less suited for the university environment because of size and nature. Most of the activities focus on the sectors of medicine and biology, various physical and chemical areas, and a few disciplines of the humanities and social sciences.

In addition, some Max Planck institutes carry out service functions by operating very expensive and sophisticated equipment, not only for their own purposes but for a wider circle of scientists not directly connected with the Max Planck institutes--for instance in the fields of astronomy, radio astronomy, and solid state physics.

The MPG has about 10,000 full-time employees, of whom approximately 2700 are scientists and 2800 are members of the technical staff. In addition, there are approximately 1700 guest scientists and scholarship holders from Germany and 1000 from abroad working at the institutes for various periods of time, the average being about 8 months.

Another organization, the Fraunhofer Society for Advancement of Applied Research (Fraunhofer-Gesellschaft zur Förderung der Angewandten Forschung) provides an important transition between basic research and application of the resulting technology. The society operates 29 institutes of its own and carries out commissioned research and technological development in the natural sciences.

An important part is also played by a number of large scientific foundations in West Germany. Three of the most prominent of these are the Volkswagen Foundation, the Fritz Thyssen Foundation, and the Donors Association for German Science (Stifter-Verband für die Deutsche Wissenschaft). Often these foundations initiate projects and new developments that are later taken over by governmental agencies.

Finally, the German Ministry for Technology and Research (Bundesministerium für Forschung und Technologie, BFMT) supports programs and projects between academia and industry. BFMT attempts to shorten the path between basic research and the application of technology. If the industry later realizes a profit from any product developed under a BFMT-sponsored project, they are required to reimburse the Ministry for the research money that went into the development of the product. For more information concerning general aspects of research support in West Germany, see *ESN* 38-3:150 (1984).

## 2 BIOMATERIALS RESEARCH

The biomaterials research area has increased significantly in the last decade. Before getting into the specifics of the German research in this area, it is useful to stop and define just exactly what is and what is not meant by the term "biomaterial."

A biomaterial is considered to be any material or substance, either natural or synthetic, that is introduced into a human (or other animal) body for the purpose of measuring, treating, or otherwise modifying some function of the

body. Thus, any artificial limbs, joints, organs, or tissue substitutes, and all of their constituents are biomaterials. So too, blood taken from one person and given to another becomes a biomaterial for the recipient. All types of wound dressings, sutures, implants, drugs, artificial teeth, etc., are biomaterials. Items constructed from biological material (plant or animal) but used in ways other than introduction into the body are not biomaterials.

All substances must meet certain general criteria if they are to be considered as biomaterials. First, and most importantly, the material must be biocompatible. That is to say, it must not be toxic to the body nor cause an allergic (immune) reaction or irritation. Secondly, the material should be stable if it is to last for a long time; or if meant to be temporary, it must degrade into products that are biocompatible. Finally, in the case of materials used as replacements for tissue, the strength and other properties of the material should be as close as possible to that of the tissue being replaced.

In West Germany, research in biomaterials seems to be concentrated in several medical school-university complexes, with little or nothing being done in such places as the Max Planck institutes or the institutes of the Fraunhofer Society. The scope of the research will be examined under the following general topic areas: wound healing and tissue repair, drug delivery, prosthetics, and miscellaneous.

#### Wound Healing and Tissue Repair

The closure of wounds and the repair of damaged tissue is an essential part of both surgery and general trauma care. Rapid healing of wounds--whether caused by surgery, accidents, or military operations--is crucial to the prevention of infection and the return of the patient to full function. Many complications can arise due to suture material: for example, fistulas can form. Tissue around wounds can separate, and massive bleeding can occur if there are deficiencies in blood clotting factors.

A number of alternatives to sutures have been tried, the most notable being synthetic tissue adhesives based on acrylic-acid derivatives (Crazy Glue is a good example of this class of adhesive). These did not fulfill the requirements and even presented some undesirable side effects. One of the most active German biomedical research groups, the Institut für Experimentelle Chirurgie (IEC) der Technischen Universität München (the Institute for Experimental Surgery of the Technical University of Munich), has been working intensely on an innovative biological seal based on blood-clotting factors and a fibrinolytic inhibitor (see *ESN* 38-11: 569 [1984]). The head of the research team, which is located in a large hospital associated with the Technical University Medical School, is Prof. Dr. med. G. Blümel.

The technique being used in Munich is called fibrin adhesion or fibrin gluing. The fibrin glue consists of two materials: deeply frozen, noninfectious fibrinogen and thrombin from human plasma. The fibrin adhesion technique imitates the final step in the coagulation of blood and the beginning of the initiation of healing in wounds. In this process, fibrinogen is converted to fibrin by thrombin, and the polymerized fibrin is stabilized by factor XIII. Fibrin sticks to the tissue and the blood begins to clot. The fibrin network formed in a wound appears to act as a scaffold for the healing of that wound, attracting large migrating fibroblasts and promoting the formation of granulation tissue.

Many procedures have been tried using the fibrin adhesive technique. It was found, however, that the fibrin seal is broken down by proteolysis, and the glue dissolves faster than the tissue can repair itself. There are, however, several fibrinolysis inhibitors, which, when applied directly to the wound area, protect the fibrin from premature lysis. Notable among these inhibitors are aprotinin and tranexamic acid. The inhibitor is mixed with the thrombin.

The IEC group has used the fibrin adhesive technique very successfully for teeth extractions, tonsillectomies, and other surgery on patients with severe bleeding disorders. They have used it for nerve anastomosis (rejoining of severed nerves), fixation of loosened joint cartilage and small cortical and cortico-cancellous bone fragments, replacement of large skeletal defects in combination with autologous cancellous bone grafts, treatment of skin ulcers of various types, treatment of burns and sealing of blood vessels and intestines. The group has also used fibrin glue to successfully repair ruptured Achilles tendons, a condition appearing frequently in physically active individuals.

The fibrin adhesive technique also has proven to be of tremendous value in liver, kidney, and spleen surgery. Following either surgery or traumas to these organs, the technique has been used to seal functional defects. It is especially useful since suturing is almost impossible in the liver and spleen.

In general, the technique of fibrin adhesion cannot replace surgical suturing; it can be a helpful adjuvant in surgery, especially in patients with bleeding disorders, and is thus a particularly useful biomaterial.

In yet another twist, the IEC group has combined the fibrin glue with collagen "sponges" or foam. Fibrin has a natural affinity for collagen. The hemostyptic effect of fibrin glue in combination with collagen has been tested *in vivo* using rats treated with the anticoagulating agent coumadin. In hemihepatectomy (excision of half the liver) or laceration experiments, it was found that the combination technique resulted in a lower death rate than when fibrin seal or collagen foams were used separately.

The research group has found that when the fibrin adhesive has been used to seal various tissues, either alone or in combination with sutures, the resulting joints have a higher tensile strength than when the adhesive is not used. Use of the glue also means that

sutures can be placed further apart, lessening damage due to tight sutures.

Another area of biomaterials research at IEC Munich has been in the treatment of burn wounds. Here again, fibrinogen and thrombin were used, being sprayed onto the wounded area. In addition, various types of split thickness skin grafts combined with the fibrin adhesive were also tried. Another approach has been to prepare special burn dressings from bovine collagen and use them for skin replacement. After a period of time (days to weeks) the collagen is resorbed, and the need to remove or replace dressings is eliminated. In all of the above biomaterials-oriented burn studies, the group is finding that the treatment is superior to classical methods.

At the Orthopädische Universitätsklinik und Poliklinik in Homburg, where Prof. Dr. H. Mittelmeier is director, research has been carried out on the use of a combination of collagen and apatite for the regeneration of bone. This research has grown out of a need to find a suitable way to enhance the regrowth of bone other than through the use of autologous, allogenic, or xenogenic grafts, each of which has disadvantages. In a recent publication, this group reported on their work with rabbits in which they studied bone regeneration aided by finely dispersed and distributed small hydroxyapatite particles (Katthagen and Mittelmeier, 1984). The hydroxyapatite particles were held in a carrier medium consisting of denaturated, depolymerized, and lyophilized collagen produced from pig skin. They found that this biomaterial, called Collapat, greatly enhanced the rate of bone formation into bore holes made in the femoral condyles.

The mechanism of bone healing through collagen-apatite is not yet clear, and many questions remain to be answered. This experiment showed that there was actual osteoinduction occurring and gave substantial credence to a large number of clinical observations that have been made over the past few years. Approximately 300 patients have had this material implanted in them at



the hospital in Homburg in the last 6 years. Results have been good, and no adverse effects have been observed.

One of the distinct advantages that this and other clinical research groups have in Germany, and several other European countries, is a relatively liberal policy regarding experimental methods with human subjects. Apparently there is no inhibition to the use of new techniques in clinical research if the patients are properly informed and give consent. In the case of the fibrin glue, for example, more than 2000 patients were treated with it while it was still in the research stage and before it became commercially available.

Likewise, it is much easier to obtain tissue from cadavers. Although it is not mandatory that the physician inform the next of kin when an organ or some other tissue is going to be taken, it is always done, according to several medical researchers interviewed.

#### Drug Delivery Research

In military medicine it is often desirable to quickly cover a wound, minimize the chance for infection, and increase the rate of healing. Several approaches have been taken to this problem, which essentially involves delivery of antibiotic and other drugs to the site of the wound by incorporating them in suitable biomaterials. Blumel and his coworkers at the IEC in Munich have developed two types of collagen sheets that can carry drugs and biodegrade without leaving toxic by-products. Both forms of the collagen are prepared from pure bovine collagen. One is in the form of a thin (about 1/16 inch), clear sheet, which allows the attending physician or nurse to view the wound. The other looks a bit like a sheet of styrofoam; it is white, opaque, and about 3/32-inch thick. The thin, transparent material can also be used quite well for burns, as mentioned above. In application, it is first soaked in water for a few minutes until it becomes pliable. Then it can be placed over the wound, conforming to the contours of the body. It "breathes," so air can pass

through but dirt is kept out. Although it requires the addition of external moisture from time to time, it has the advantage that it does not have to be removed--a major problem in the course of treating burn injuries because fragile skin is often removed along with the bandage. The collagen film also provides a "bridge" for the growth of new skin.

Both of the forms of collagen can be impregnated with drugs. The researchers have chosen to use gentamycin, a broad-spectrum antibiotic that is effective against a wide range of gram-negative bacteria (such as *E. coli*, *Klebsiella*, *Pseudomonas*) as well as certain gram-positive ones (especially staphylococci). Gentamycin has a bactericidal effect on proliferating and resting pathogens.

The thicker collagen can also be used for burns and for other types of wounds, such as massive cuts or tears of the skin. It can hold more drug and thus release it over a longer period of time. This material can also be implanted into and around bone during surgical treatment for osteomyelitis and other diseases in which there is a high likelihood of localized infection. The collagen is completely resorbed by the body over a period of weeks to months, and the drug is delivered during the lifetime of the collagen. Since the US Navy does not have enough skin-graft material to meet even peacetime needs, this line of research may have potential value to the tissue-bank program.

Infection is a potential problem in many types of trauma cases in military medicine. One type of infection, osteomyelitis, is of particular importance because many major fractures are treated surgically, and in military operations there are a large number of severe injuries with extensive damage to soft tissues. Even in the best of operational settings and hygienic conditions, it is not possible to always avoid serious complications due to infection. The rigid matrix of the bone provides a good site for the growth of bacteria, especially in areas where blood supply is diminished. Chemotherapeutic agents,

administered systemically, cannot penetrate into dead bony tissue. It is most often necessary to surgically remove or clean out the infected area and place large quantities of antibiotic directly at the site of the infection.

At the B.G. Unfallklinik (Emergency Clinic) in Frankfurt, a team headed by Prof. Dr. med. H. Contzen has developed another unique delivery system for antibiotics which is being used to treat chronic osteomyelitis and other types of infection. Contzen and his coworkers have incorporated gentamycin in 7-mm-diameter beads of polymethylmethacrylate (PMMA). Each bead contains 7.5 mg of gentamycin sulfate as well as 20 mg of zirconium dioxide as a radiographic contrast medium. These beads are being marketed by Merck under the name Septopal. Septopal has been registered in all European countries and most South American countries and has recently been admitted by the US Food and Drug Administration for investigation of a new drug.

In use, the PMMA beads, containing the antibiotic, are usually strung together on a strand of multifilament surgical wire to form a string of 10, 30, or 60 beads (Figure 1). In the case of infected bones, the string (of suitable length) is surgically implanted into the bone cavity and left in place for 7 to 10 days (Figure 2). The last bead is often left protruding through the skin to facilitate removal, which is done by pulling the remaining chain out using a slow steady force. The chains are not left in longer because of the danger of connective tissue ingrowth.

There are several reasons that gentamycin is the antibiotic of choice for combination with PMMA, or collagen as used in Munich and Garmisch:

- It is a broad spectrum antibiotic
- Very few pathogens can resist it
- The development of subsequent resistance is infrequent
- There are essentially no allergic reactions to it
- It has good stability, even at high temperatures
- It has good solubility in water.

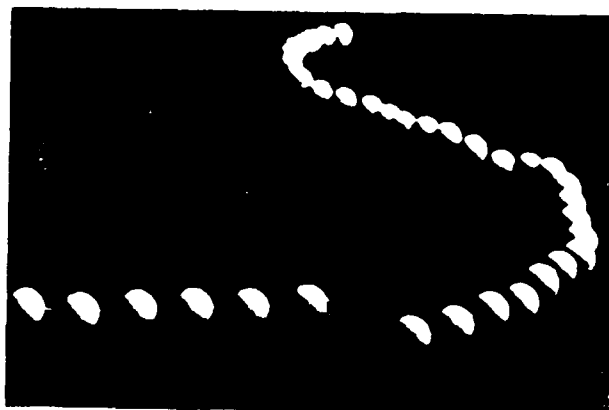


Figure 1. Gentamycin-PMMA beads. The beads are spherical, with a diameter of 7 mm. They are supplied singly, or strung on a metal wire in units of 10, 30, or 60 beads.



Figure 2. Gentamycin-PMMA beads implanted in the cavity of an infected femur.

The use of PMMA as a carrier for gentamycin has several advantages. First of all, it permits a protracted release of the drug in bactericidal concentrations at the site of infection (Figure 3). Secondly, the gentamycin does not infuse into the serum in spite of high local concentrations.

The local implantation of Septopal chains in infected bone and soft tissue cavities permits a very effective local antibiotic treatment, independent of the extent to which the surrounding tissue is supplied with blood. The release of the antibiotic gentamycin from Septopal beads takes place directly at the site of the infection by diffusion in concentrations which far exceed the minimum inhibitory concentration for the causative organisms.

One of Contzen's coworkers, Dr. Klaus Klemm, has reported successfully using Septopal chains to cure chronic bone infection and infected pseudarthroses (Klemm, 1983). He has done cancellous bone grafting into areas that were formerly quite infected but cleared up with the use of the beads. In fact, since 1973 almost 2000 cases of local infection have been treated with Septopal chains. This seems characteristic of a number of German laboratories that I visited, indicating a lead-time of 5 to 10 years or more over the US for the introduction of a medication or therapeutic technique.

Other clinical research institutes were found to be heavily engaged in research similar to that in Frankfurt, with similar results. Dr. Helmut Wahlig of the Department of Medical Microbiology at Merck in Darmstadt, has reported on the development of a miniature version of the Septopal beads (Wahlig and Dingeldein, 1983). These mini-beads are 3.5 mm in diameter and are being used in situations where the normal beads are too large--hand surgery, face and oral surgery, and pediatric cases.

At the Unfallchirurgische (Accident Surgery) Klinik und Zentrum für Chirurgie of the University of Giessen, Prof. Ecke and his staff have tried another

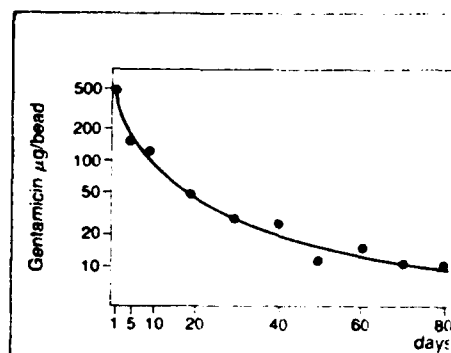


Figure 3. Gentamycin release from septopal beads ( $\mu\text{g}/\text{bead}/\text{day}$ ) over a period of 80 days.

tack in trying to combat osteomyelitis (see Schultheis, et al., 1981). They have recognized some shortcomings in the PMMA delivery system and have incorporated gentamycin in a fast-hardening amino acid solution, Ethibloc (being produced by Ethicon Company, Hamburg). This biomaterial has several distinct advantages over the PMMA. It is not necessary to remove any portion of it as is the case with the Septapol beads. It does not leave a cavity, but rather is resorbed or replaced with fibrous tissue. In tests on rats, the Ethibloc has been injected into the marrow cavity of the femur. After 41 days, there was still antibiotic activity at the site of the injection. This work continues, and human trials have been in progress for about 2 years.

Schultheis also has used Ethibloc as an embolizing agent and drug carrier in the treatment of several types of tumors (Schultheis et al., 1982, and Schultheis, 1983). With this technique, the arterial blood supply to the tumor is blocked by the embolizing agent and at the same time a cytostatic agent is slowly released. There are several indications for this type of "chemoembolization," as Schultheis calls it--for example, it can be used preoperatively to reduce the size of the tumor or postoperatively to kill any remaining tumor tissue. The technique is especially suited to urological, gynecological,

gastroenterological, and bronchial tumors, as well as of tumors of the head and neck.

There are several other laboratories in West Germany that are very active in the use of these and other biomaterials in drug delivery. Notable among these are:

Department of Traumatology  
Berufsgenossenschaftliches Unfallkrankenhaus  
Hamburg

Orthopädische Universitätsklinik  
Munster

Surgical University Clinic and Policlinic  
Munich

Surgical Department  
Jung-Stilling-Krankenhaus  
Siegen

Department of Surgery  
Bundeswehrzentral Krankenhaus Koblenz  
Koblenz

Centrum Chirurgie Klinikum der Universität  
Frankfurt am Main

At the Department of Traumatology, University Hospital for Surgery in Cologne, Dr. med. J. Eitenmüller and colleagues have been very active in research using hydroxyapatite granules to contain and deliver antibiotics. In their studies with dogs, they found that the ceramic granules were superior to other methods for delivering antibiotics or antiseptics in the treatment of osteomyelitis (Eitenmüller et al., 1984, 1985).

#### Prosthesis

One of the most active areas of biomaterials research is that dealing with artificial limbs and organs. The basic research aspects of these devices most often center around the interactions that take place at the interface

between the implanted device and the body tissue. It is not enough for the constituent material to be biocompatible in the sense given earlier, often it must have very specific properties. For example, the material used for artificial blood vessels or in heart chambers and other places where it comes into contact with blood must not allow the blood to adhere as this leads to the formation of clots. On the other hand, material used for grafting bone should have a good affinity for bone, and even promote the ingrowth of new bone into it. In the latter case we might think of the material as being tissue-philic and in the former case, tissue-phobic.

The implantation of artificial joints--particularly hips, knees, and elbows--is becoming a major orthopedic procedure. One of the primary problems with the implantation of hip joint prostheses has been the aseptic loosening of the joint at some point following the replacement surgery. This may occur at any time from a few months to a few years later. In West Germany there are two new advances that may have a significant impact on hip-joint surgery.

The usual procedure for attaching the joint is to cement it in place in the femur. This cement often gives way as it "ages," and surgery is usually required to re-cement the joint. At the University of Giessen School of Medicine, Prof. Dr. med. Ecke heads a research team that is studying an entirely new way to hold the joint in place. Using computer simulation, they have devised a cementless joint with a raised portion that acts as a resistive point and does not allow the joint to come loose once it has been screwed into the femur. This new prosthesis is being tested in the clinic at Giessen and at several other clinics in West Germany. According to Ecke, not one joint has loosened out of about 200 implanted thus far. This is not an example of a new biomaterial, but of a new method of fabricating an existing material.

Another example was found at the Orthopädische Universitätsklinik und

Poliklinik in Homburg, where H. Mittelmeier is director. More than 25 years ago, Mittelmeier suggested that an increase in the surface area of the stem of the hip prosthesis would solve the problem of loosening of the implant. He reasoned that this would promote the ingrowth of bone and improve the distribution of forces below the critical resorption threshold, thereby effecting a balance between load and structure and preventing prosthetic loosening. He and his colleagues proposed to accomplish this by incorporating projections and recesses into the prosthetic surface, and by replacing PMMA, most frequently used then, with a fracture- and wear-resistant biomaterial (metal-on-polyethylene, later abandoned in favor of aluminium oxide ceramic).

Over the years, the group in Homburg has studied the somewhat controversial problem of "cement aging" due to fatigue. They have found that there is a steady decline in the strength of the cement up to about 15 million load cycles (1 year equals approximately 1 million cycles). This, they believe, accounts for the frequent failure of cemented prostheses after several years of service.

The two prostheses that Mittelmeier and his colleagues have developed are shown in Figure 4, and are known as Autophor. The design on the left, known as Type I, is made of cobalt-chromium alloys and has parallel ridges cut along the stem to distribute the load. In use, bone tended to grow into the depressions and provide a good tight fit. In theory, the device should fit tighter and tighter with time if implanted into a young to middle-aged person.

Their Type II, shown on the right, is made of a high-strength cobalt-chromium cast alloy known as "Endocast" and manufactured by Krupp AG of Germany. It has twice the fatigue strength of the traditional Co-Cr alloys and is more corrosion-resistant than stainless steel or titanium alloys (Mittelmeier, 1984).

During the past 10 to 20 years, various groups of German manufacturers

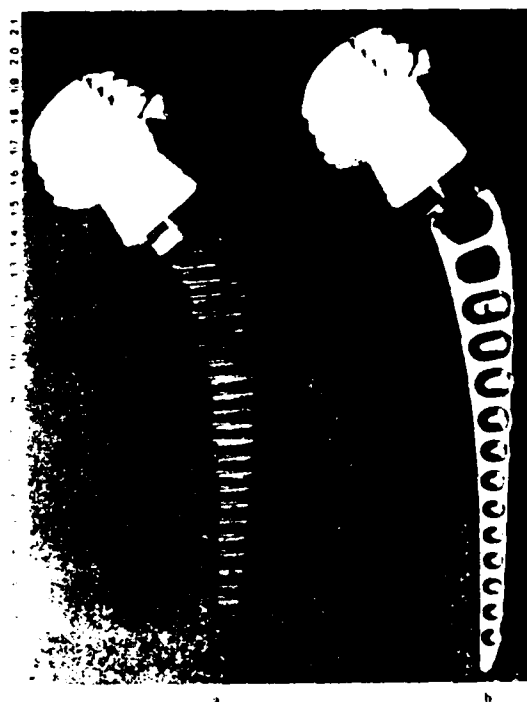


Figure 4. "Autophor" ceramic and cobalt-chromium hip prostheses, developed by Ecke: (a) Type II stem with transverse bearing ribs, (b) Type II stem with depressions into which new bone grows.

and clinicians have done extensive research on the use of aluminum oxide ceramic as a prosthetic material (Dörre et al., 1975; Mittelmeier et al., 1980; Griss et al., 1973; Salzer et al., 1975). The research in Homburg centered around a ceramic known as "BioloX," manufactured by Feldmühle AG. This is used for the "head" of the device, consisting of the ball and its socket.

BioloX is an aluminum oxide ceramic with an  $\text{Al}_2\text{O}_3$  content of 99.7 percent and a maximum grain size of 4 microns. The prosthetic components are produced from polycrystalline powder by sintering. BioloX has certain advantages, such as purity, density, and small grain size, that make it ideal. Its surface can also be polished to a perfect smoothness, a feat not possible with metal surfaces. A further advantage is

found in the extremely low wear, which is only about 1/10 to 1/20 of that of the metal-polyethylene that has been used very widely. Laboratory tests have shown that the ceramic material should retain its excellent wear resistance for several decades, and perhaps for a lifetime.

There have been a number of biocompatibility experiments of the ceramic involving cell cultures, and test implantations in rats and rabbits have shown it to be very compatible (Harms and Mausle, 1980; Griss et al., 1973).

The cementless Autophor system is of interest to military medicine because it lends itself best to applications in younger people, who are generally considered poor candidates for standard cemented prostheses since they have a long life expectancy. Cemented prostheses are now being reserved for older patients who are not likely to live long enough to outlast the cement.

At the Garmisch-Partenkirchen Hospital, a team headed by Prof. Dr. med. F. Lechner has attacked the problem another way. Dr. R. Ascherl of his group, who has a lot of experience with the use of electrical stimulation of bone growth, realized that the interface between the surface of the implant and the bone resembles a nonunion and thus might be looked upon as a type of pseudarthrosis between biomaterial and osseous (bony) tissue.

For the past 11 years, Ascherl and coworkers have conducted a study involving more than 600 patients with cemented prostheses who were scheduled for reoperation to correct a loosening joint. They treated the patients with the same pulsing magnetic field that is being used for bone stimulation. Adjustable and specially shaped coils were placed around the hip joints, and treatment was given 2 to 4 hours per day for an average of 15.4 weeks. The results of the treatment were measured in terms of the level and occurrence of spontaneous pain, pain while walking, use of crutches, distance of walking, and dosage of pain killers required. Excellent

results (painless walking without crutches) were obtained in 26 percent of the patients. Good results were shown for a further 41 percent of the group. There was no improvement in 33 percent, who then went on to have further surgery; some prostheses had to be reimplanted. Thus, 67 percent of the patients avoided surgery through the use of the pulsing electromagnetic fields. The maximum follow-up has now been 11 years, and there have been no recurrences of loosening joints in most of the treated cases. This type of treatment seems to be indicated and most successful in cases with a painful loosening soon after implantation. Septic loosening, fractured cement, and dislocation of the implants have to remain the domain of surgery.

Recently, Ascherl, who also works in Blumel's group at IEC Munich, has experimented with a new biological prosthesis made from tendon and ligament tissue. He and his team (Ascherl et al., 1985) have developed a preservation procedure whereby they can take ligaments and tendons from one animal, preserve the tissue for a time (several days, at present), and later use it to replace ligaments and tendons in another animal. The preserving agents they use are primarily dicarboxylic acids, ficine and tetrahydric furane. Initially, their experiments started with rabbits, replacing a ligament of the hind leg and a tendon of one of the flexor muscles. In their first study, 25 rabbits received a ligament prosthesis using the preserved tendon. Fixation was by way of small instrumentation screws and washers.

After 3 months, the rabbits were sacrificed and the results examined by: (1) macroscopic and microscopic morphology, (2) microradiography, and (3) biomechanical testings. The collagenolytic activity was assayed by the degradation of tritium-labeled collagen type I with prosthesis-incubated modified medium. There was no evidence of joint damages or instabilities and no allogenic reactions. Seventy-five percent of the ligament prostheses were ensheathed by

fibrous connective tissues and showed good ingrowth at the suture lines. The balance were partly degraded and partly substituted through ligament-like connective tissue. There was a slight decrease in the breaking strength.

Some similar experiments have also been carried out in sheep using preserved calf tendons to replace knee ligaments. The results were very encouraging, with good attachment to the bone and good biocompatibility. It appears from these early animal experiments that this group in Munich is well on the way to solving another crucial biomaterials problem that occurs often in sports and other physical activities, such as military operations.

Another type of ligament replacement is being tried by Ecke at the University of Giessen (Ecke, 1985). They have taken part of the ligament of the kneecap, combined it with a resorbable suture material (polydioxanone), and used it to augment damaged anterior cruciate ligaments (which attach the femur to the tibia). They have so far studied more than 15 patients with excellent follow-up after more than 33 months. They have also used another resorbable suture material, polyglactin 910, for the replacement of knee ligaments in three animal studies involving rabbits and sheep. In some cases, results were very good, but in others not too encouraging. These are examples of autologous substances being mixed with a synthetic material to form a biomaterial.

Ascherl (in Munich) has experimented with carbon fiber reinforced resin (CFRR), a new biomaterial, as the material for making the cup of a hip prosthesis. He used ceramics for the ball and steel alloy for the stem. Using dogs, he studied the ingrowth of bone into the outer surface of the cup and found it to be very good, as was the biocompatibility. Carbon fiber composites are already in use, and this represents a departure in a continuing attempt to find a better biomaterial for use in fabricating the parts of the joint implants. A number of other laboratories in West Germany are studying

the use of carbon fibers as biomaterials. I learned of research at the University of Ulm, but was unable to visit them to get more information. It is interesting to note that the CFRR has been used also in machinery and space technology.

#### Miscellaneous Implants

There are a number of situations calling for implants in trauma medicine, especially in orthopedic medicine. Here the science of biomaterials again plays a major role. This area has called upon the talents of the metallurgist, the chemist, and the biomedical engineer. For many years, the most widely used material was stainless steel, due primarily to its strength and high resistance to corrosion. Titanium has been widely used, either alone or in combination with other metals. During the past 10 to 20 years, ceramics have come to be the material of choice in many situations previously the domain of metals. West German scientists, physicians, and bioengineers are considered to be in the forefront of research into the use of ceramics as biomaterials. In large measure, the ceramics get most of their use in oral reconstruction, following either trauma or surgery to the jaw and teeth. Ceramics are also now considered the material of choice for those applications such as the ball and cup of the hip and elbow joints. These are places that are subject to a lot of wear. Ceramics generally wear better than metal and give off fewer particles due to friction. In those areas where ingrowth of tissue is desired, ceramics again are used since the porosity can be controlled during its manufacture, and tissue ingrowth is highly dependent upon porosity (see ESN 39-6:247 [1985]).

German physicians and bioengineers have developed a number of unique orthopedic methods, as has been mentioned. One reason for their success may be the freedom they have in trying new ideas on patients. As early as 1940, Gerhard Kuentscher developed a technique for stabilizing fractures of the femur.

Kuentscher's original technique called for placing a long steel "nail" in the entire length of the intramedullary canal of the femur. He later improved upon this technique by making an interlocking nail. This called for screws passing through the bone shaft and through the nail to hold it in place (Figure 5). The interlocking nail was developed in collaboration with Dr. Klaus Klemm and Dr. H. Schellman at the B.G. Unfallklinik in Frankfurt (Klemm, 1977).

The use of Kuntscher's interlocking nailing method as modified by Klemm and Schellman allows for the stabilization of fragmented fractures, spiral fractures, severely comminuted fractures, and transverse fractures in bone segments with wide medullary canals. The great degree of stabilization can be attributed to the use of fixation screws proximal and distal to the fracture site, anchoring the nail to the bone segments capable of bearing the load (see Figure 1). Furthermore, the design of the interlocking nailing system eliminates the threat of stress concentrations, distributing these disruptive forces throughout the length of the nail. The main advantages of the interlocking nail are as follows: it permits early weight bearing; opening of the fracture site is not necessary, therefore there is less danger of devitalization of bone fragments; infection is less likely to develop; and removal of the nail is a minor procedure compared to removing a plate.

This technique, first developed in Germany, is now in use throughout the Western world. The technique that lends itself well to some of the types of leg fractures that are likely to occur during military operations.

### 3 SUMMARY

West Germany is one of the leading countries in Europe for research in biomaterials. Researchers have developed a number of new techniques and methods utilizing a wide range of synthetic and

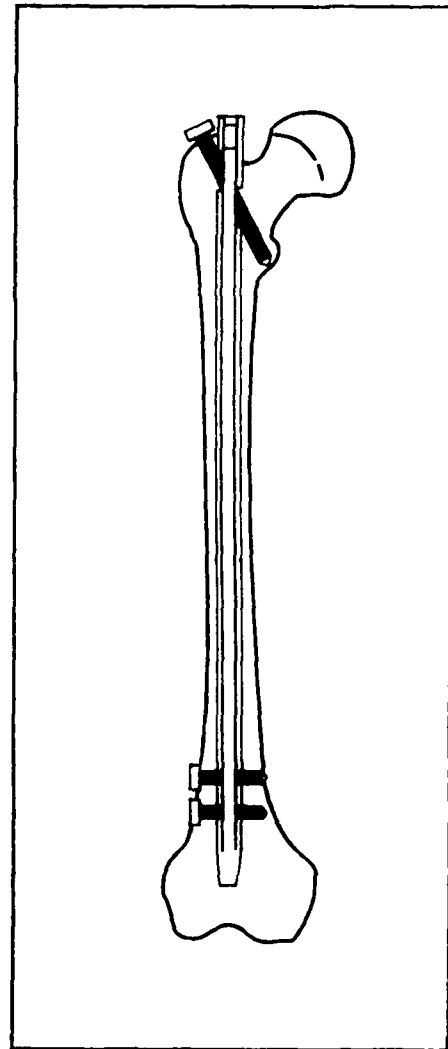


Figure 5. The "interlocking nail" developed at the B.G. Unfallklinik. Note the screws that hold the nail in place.

natural materials for use in medicine. Exotic ceramics, metals, and plastics are being used both in animals and in humans for such things as tissue repair, wound coverings, drug delivery, and prostheses. The West German scientists, bioengineers, and clinicians are very aggressive in attacking new problems related to the use of biomaterials in therapy.



## References

- Ascherl, R., W. Siebels, B. Kobor, K. Geissdörfer, B. Adelman, H. Lichti, W. Fraefel, and G. Blümel, "Bioprosthesis in Ligament Replacement--An Experimental Study" (Presented at the 11th Annual Meeting of the Society for Biomaterials, San Diego, California, 25-28 April 1985).
- Dörre, E., H. Beutler, and D. Geduldig, "Anforderungen an Oxidkeramische Werkstoffe als Biomaterial für Künstliche Gelenke," *Arch. Orthop. Unfallchir.*, 83 (1975), 269.
- Ecke, H., personal communication, 1985.
- Eitenmüller, J., G. Peters, W. Golsong, R. Weltin, G. Gellissen, and W. Reichmann, "Die Freisetzungverzögerung von Polyvinylpyrrolidon-Jod-Komplex aus Porösen, Resorbierbaren Trikalziumphosphat-Keramikgranula Durch die Verwendung Loslicher Überzüge zur Lokalen Behandlung der Osteomyelitis," *Unfallheilkunde*, 87 (1984), 517-523.
- Eitenmüller, J., K.H. Schmidt, G. Peters, G. Gellissen, R. Weltin, and W. Reichmann, "Experimental and Preliminary Clinical Experience With Absorbable Calcium Phosphate Granules Containing an Antibiotic or Antiseptic for the Local Treatment of Osteomyelitis," *Journal of Hospital Infection*, 6, Supplement (1985), 177-184.
- Griss, P., B. Krempien, H. von Andrian-Werburg, G. Heimke, and R. Fleiner, "Experimentelle Untersuchung zur Gewebeverträglichkeit Oxidkeramischer ( $Al_2O_3$ ) Abriebteilen," *Arch. Orthop. Unfallchir.*, 76 (1973), 270.
- Harms, J. and E. Mausle, "Biokompatibilität von Implantaten in der Orthopaedie," *Heifte Unfallheilkd.*, 144 (1980), 1-118.
- Katthagen, B.-D., and H. Mittelmeier, "Experimental Animal Investigation of Bone Regeneration With Collagen-Apatite," *Arch. Orthop. Trauma Surg.*, 103 (1984), 291-302.
- Klemm, K., "Experience With the Interlocking Nail," *Medical Bulletin*, 34 (1977), 299-301.
- \_\_\_\_\_, "Indications for Septopal-Chains in Chronic Bone Infections and Their Clinical Application," *Polymers in Medicine*, Vol 13, No. 1-2 (1983), 37-50.
- Mittelmeier, H., "Total Hip Replacement With the Autophor Cement-Free Ceramic Prosthesis," in *The Cementless Fixation of Hip Endoprostheses*, ed. E. Morscher (Berlin, Heidelberg: Springer-Verlag, 1984), 225-241.
- Mittelmeier, H., U. Hanser, and J. Harms, "Zur Lösung des Zementproblems mittels Apatit-Carbonfaser-Knochenzement," *Z. Orthop.*, 118 (1980), 658.
- Salzer, M., K. Zweymüller, H. Locke, H. Plenk, Jr., and G. Punzet, "Biokeramische Endoprothesen," *Med. Orthop. Techn.*, 95 (1975), 40-45.
- Schultheis, K.-H., "Chemoembolization: A New Treatment for Malignant Tumors and Metastases," in *Recent Results in Cancer Research*, 86 (Berlin & Heidelberg: Springer-Verlag, 1983), 46-47.
- Schultheis, K.-H., K. Henneking, K.E. Rehm, H. Ecke, H.G. Schiefer, and H. Breithaupt, "Untersuchungen über die Freisetzungskinetik Verschiedener Chemotherapeutika aus einer Viskosen, im Feuchten Milieu Schnell Aushärtenden Aminosäurenlösung und Ihre Mögliche Klinische Anwendung," in *Lagenbecks Archives de Chirurgie*, Supplement (1982), 199-205.
- Schultheis, K.-H., A. Schulz, and H.-G. Schiefer, "Fast Hardening Aminoacid-solution as Potential Carrier of Chemotherapeutic Agents in the Treatment of Chronic Osteomyelitis," *Unfallchirurgie*, 7 (1981), 324-333.
- Wahlig, H., and E. Dingeldein, "Antibiotics and Polymethylmethacrylate--An Effective Drug Delivery System in Orthopaedic Surgery," *Proceedings of the 13th International Congress of Chemotherapy* (Vienna, 1983), 1-5.

**END**

**FILMED**

**11-85**

**DTIC**